REMARKS

Claims 26, 27, 32, 33, and 37-114 are pending in the present application.

Interview Summary

A. Interview of July 2, 2003

The Applicants would like to thank Examiner Canella, Caputa, and Stanton for their time and the courtesy of the telephonic interview on July 2, 2003. During the interview, Melief et al and de Boer et al (5,874,082) were discussed and differentiated by Dr. Antler. Examiner Stanton suggested that Ex. Canella vacate the previous Office Action dated June 4, 2003 and provide the Applicants with a revised Office Action. Examiner Stanton indicated to Ex. Canella that the revised Office Action should contain minor rejections and should streamline and clarify any rejections.

B. Interview of February 12, 2004

The Applicants would like to thank Examiner Canella for her time and courtesy during the telephone interview on February 12, 2004 and for review of the Draft Amendment sent to the Examiner on February 11, 2004. The Examiner indicated that the enablement and written description rejections had been successfully overcome by the Applicants based on the amendments to the claims and the remarks in the Draft Amendment sent to the Examiner on February 11, 2004. Particularly, the Examiner indicated that the multiple dependency rejection had successfully been overcome (further discussed in para. 2 of the present Amendment). The Examiner indicated that the amendments to claims 60 and 61 to remove reference to a trade name successfully overcame the Examiner's indefinite rejection (further discussed in para. 3 of the present Amendment). The Examiner indicated that the amendment to the claims to remove the language "preventing" overcomes the Examiner's enablement rejection (further discussed in para. 4 of the present Amendment). The Applicants and the Examiner agreed that claim 49 would be canceled, without prejudice, overcoming the Examiner's enablement rejection (further discussed in para. 5 of the present Amendment). The Examiner indicated that amendment of claim 37 to recite "an antibody" apparently overcomes the Examiner's written description rejection (further discussed in para. 6 of the present Amendment).

Also during the interview, the claims were discussed and distinguished over Melief et al and de Boer (US Patent No. 5,874,082) with the Examiner. The Examiner and the Applicants discussed the language in the independent claims "increases binding of CD40 ligand to cell surface CD40 on B cells by at least 45%" with regards to Melief et al and de Boer. The Examiner indicated that this language appears convincing over Melief et al and that de Boer was a secondary reference to Melief et al. The Applicants and the Examiner agreed that the Applicants would further address Melief et al, particularly Figure 3 of Melief et al, in the present Amendment.

1. **Para. 6 of the Office Action – Objection to Embedded Hyperlink**

The Examiner objected to the specification because it contains an embedded hyperlink and/or other form of browser executable code on page 31, lines 12 and 33, page 32, line 5 and page 46, lines 1 and 3. The Examiner suggested that the hyperlinks be deleted from the specification.

The specification has been amended to remove the hyperlinks. Care has been taken so that no new matter has been added. The Applicants respectfully assert that this objection has been successfully overcome.

2. **Para. 7 of the Office Action – Multiple Dependant Claims**

The Examiner objected to claims 67, 69-74, and 81 for allegedly being of improper form because a multiple dependent claim cannot serve as the basis for other multiple dependent claims.

As discussed during the interview of February 12, 2004, claims 67, 69-74, and 81 have been amended so that they are not in multiple dependent form and the Examiner indicated that the multiple dependency objection appeared to be successfully overcome. The Applicants respectfully assert that this objection has been successfully overcome.

3. **Para. 8 of the Office Action – Rejected Under 35 U.S.C. Section 112, Second Paragraph**

The Examiner rejected claims 60-62, 68, 75-80, 82, 86-89, 95, 98, 101, 104, 107, 110 and 113 under 35 U.S.C. Section 112, second paragraph, for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as their invention. The Examiner alleges that claims 60 and 61 are rendered vague and indefinite by reference to a trade name.

As discussed during the interview of February 12, 2004, claims 60 and 61 have been amended to remove reference to a trade name thereby rendering this rejection moot. Care has been taken so that no new matter has been added. The Applicants respectfully assert that this rejection has been successfully overcome.

4. **Para. 9 of the Office Action – Rejected under 35 U.S.C. Section 112, First Paragraph**

The Examiner rejected claims 27, 64, and 65 under 35 U.S.C. Section 112, first paragraph as allegedly failing to comply with the enablement requirement. The Examiner further rejected claims 32, 33, 39, 42, 52-57, 87-89, 95, 98, 101, 104, and 107 in part as they depend on claim 27. The Examiner alleges that the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention. Particularly, the Examiner alleges that the Applicants referral to the deposit of the hybridoma secreting the S2C6 antibody on page 58 of the specification is insufficient assurance that all the conditions of 37 CFR 1.801-1.809 have been met.

The Applicants provide with the filing of this Amendment a copy of an affidavit by the attorney of record in the parent application 09/328,296, of which this application is a divisional, stating that the deposit has been accepted by an International Depository authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application, and that the deposit will be replaced if viable samples cannot be dispensed from the depository. Applicants respectfully assert that this rejection of the Examiner has successfully been overcome.

5. **Para. 10 of the Office Action – Rejection of claims 26, 27, 32, 33 and 37-114 under 35 U.S.C. Section 112, First Paragraph**

The Examiner rejected claims 26, 27, 32, 33 and 37-114 under 35 U.S.C. Section 112, first paragraph, for allegedly failing to reasonably provide enablement methods for preventing cancer while the Examiner admits that the specification is enabling for methods of treating cancer.

Applicants do not concede to the Patent Office position; Applicants are amending the claims solely to obtain expeditious allowance of the instant application. Applicants

have amended claims 26, 27, 37, 58, 59, 60, 61, 63, and 64 to remove preventing. By this amendment, Applicants expressly do not disclaim equivalents of the invention. The Applicants respectfully assert that the Examiner's rejection has been successfully overcome.

6. Para. 11 of the Office Action – Rejection of claims 26, 44-46, 49, 61, 62, 75 and 78 under 35 U.S.C. Section 112, First Paragraph

The Examiner rejected claims 26, 44-46, 49, 61, 62, 75 and 78 under 35 U.S.C. Section 112, first paragraph, for allegedly not reasonably providing enablement for human antibodies which comprise SEQ ID No:2-4 and 7-10, or human antibodies comprising sequences having at least 80% amino acid identity to SEQ ID No: 8-10 or a human antibody comprising at least two CDR sequences selected from the group consisting of SEQ ID NO:8-10. The Examiner admits on page 7, lines 23-25 of the present Office Action that the application teaches at least on page 5, lines 10-14, the administration of a chimeric or humanized version of the S2C6 antibody.

The Applicants respectfully traverse this rejection. Enablement for antibodies "comprises a human immunoglobulin constant domain" as claimed in claim 26 is provided at least on pages 5 and 24-28 of the specification. The specification discloses well known techniques for the production of humanized antibodies (see, at least, page 26, lines 16-18 where U.S. Patent No. 5,585,089 to Queen and U.S. Patent No. 5,225,539 to Winter are identified, which are well known to one of skill in the art as methods which produce humanized antibodies). Pages 24-28 describe in detail, and without undue experimentation, how the CDRs can be inserted into the human framework regions.

Applicants do not concede to the Patent Office position; Applicants are canceling claims 49 and 78, which recite "a human antibody," as agreed during the interview with the Examiner on February 12, 2004, to obtain expeditious allowance of the instant application. The Applicants respectfully assert that the Examiner's rejection has been successfully overcome.

7. Para. 12 of the Office Action –Rejection of claims 37, 40, 41, 42, 44-51, and 63 under 35 U.S.C. Section 112, First Paragraph

The Examiner rejected claims 37, 40, 41, 42, 44-51, and 63 under 35 U.S.C. Section 112, first paragraph, for allegedly failing to comply with the written description

requirement. The Examiner goes on to state that allegedly the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. More particularly, in paragraph 12(A), the Examiner alleges that the claims encompass molecules which are not proteins or antibodies, and which bind to an epitope of CD40 which is not the epitope to which the S2C6 antibody binds. Applicants respectfully traverse this rejection.

Applicants do not concede to the Patent Office position; Applicants are amending the claims solely to obtain expeditious allowance of the instant application. Applicants have amended claim 37 to recite "...an antibody that immunospecifically binds CD40...."

Present claim 37 is analogous to Example 16 in the Revised Interim Written Description Guidelines. As discussed in the Revised Interim Written Description Guidelines Training Materials, available from the United States Patent and Trademark Office web page at http://www.uspto.gov/web/menu/written.pdf, "[t]here is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed." (see page 4, lines 7-8). Example 16 is directed to antibodies. (see pages 59-60 of the Written Description Guidelines). As in Example 16, the present specification teaches that CD40 (antigen X) has been isolated and is expressed on a variety of cell types, including B cell malignancies. (see at least pages 1-2 of the specification). As in Example 16, the present specification discusses the use of a CD40-Ig and soluble CD40 on at least pages 52-54 of the present specification. The present specification *goes beyond* the specification described in Example 16 and actually discloses example antibodies which bind to CD40 (i.e. S2C6) and asserts that these antibodies can be used in the treatment of cancer and immune disorders. Example 16 goes on to state that:

> The general knowledge in the art is that such antibodies are structurally well characterized. It is well known that all animals produce antibodies and they exist in five isotypes, IgM, IgG, IgD, IgA, and IgE. Antibodies contain an effector portion which is the constant region and a variable region which contains the antigen binding sites in the form of complementary determining regions and framework regions. The sequence of constant regions as well as the variable regions subgroups (framework regions) from a variety of species are known and published in the art. It is also well known that antibodies can be made against virtually any protein....The level of skill and knowledge in the art of antibodies at

the time of filing was such that production of antibodies against a well-characterized antigen was conventional. This is mature technology where the level of skill is high and advanced.

As in Example 16, one of skill in the art would have recognized the spectrum of antibodies which bind to CD40 were disclosed as a result of isolation of CD40. Therefore, as in Example 16 of the Written Description materials, claim 37 as amended to recite "an antibody," meets the requirement under 35 U.S.C. 112, first paragraph, as providing adequate written description of the claimed invention. As discussed with the Examiner during the interview of February 12, 2004, the Examiner indicated that this amendment should overcome the Examiner's rejection. Applicants respectfully assert that this amendment successfully overcomes the Examiner's rejection.

In paragraph 12(B), the Examiner rejects claims 60, 61, and 62 for allegedly lacking written description. The claims recites a protein having 95% identity to SEQ ID No:7 or 80% identity to SEQ ID NOS: 8, 9, and 10. As discussed during the interview of February 12, 2004, the Examiner indicated that claims 60, 61, and 62 should be allowable. It is well known to one of skill in the art that sequences having this percent identity would encompasses proteins having the structure of S2C6 and the functional attributed of S2C6. Applicant respectfully asserts that this rejection has successfully been overcome.

8. **Paragraph 13 of the Office Action – Rejection of Claims 26, 27, 33, 41, 42, 44-48, 50, 52-55, 59-65, 68, 75-77 and 83-93 under 35 U.S.C. 103(a) as allegedly being unpatentable over Melief et al (US Application 2003/0022860) in view of de Boer (U.S. Patent No. 5,874,082).**

The Examiner rejected claims 26, 27, 33, 41, 42, 44-48, 50, 52-55, 59-65, 68, 75-77 and 83-93 under 35 U.S.C. 103(a) as allegedly being unpatentable over Melief et al (US Application 2003/0022860) in view of de Boer (U.S. Patent No. 5,874,082). The Applicant respectfully traverses the rejection.

The Applicant respectfully directs the Examiner's attention to MPEP paragraph 707.07 on the "Completeness and Clarity of the Examiner's Action," MPEP paragraph 707.07(e) on "Note All Outstanding Requirements," and MPEP paragraph 707.07(g) on "Piecemeal Examination." Particularly, MPEP 707.07(g) states "[p]iecemeal

examination should be avoided as much as possible. The examiner ordinarily should reject each claim on all valid grounds available, avoiding, however, undue multiplication of references." The Applicants respectfully assert that in the instant application, the Examiner has had ample opportunity in previous Office Actions to cite references and make objections and rejections. The present Office Action follows an interview with Examiner Canella, her Supervisory Examiner Caputa, and Brian Stanton during which it appeared to the Applicants that the issues had been resolved. The Applicants expected any subsequent Office Action to include insignificant issues to be clarified. In opposition to the guidance provided in MPEP sections 707.07, 707.07(e) and 707.07(g) regarding completeness of an Office Action and the avoidance of piecemeal examination, the Examiner provided the present Office Action citing new references when she had ample opportunity to cite these references in previous Office Actions and contrary to what was agreed to during the interview. Applicants sincerely hope that any rejections or objections have been clarified and established in the present Office Action, as directed by Ex. Stanton, so as to avoid piecemeal examination.

> The Examiner *alleges* that Melief et al teach
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> "a method of treating cancer comprising the administration of CD40 binding molecules (abstract, claims 5-9, 11-13). Melief et al teach that the "triggering" of CD40 in vivo can replace the requirement of a T-cell helper signal (examples 1 and 2 [0045]) and concludes that CD40 activation in the presence of tumor derived peptide reverses peripheral tolerance and results in tumor specific immunity (lines 22-24 of [0045]). Melief et al teach that the CD40 binding molecules include antibodies [008] and that humanized antibodies are preferred for the treatment of human subjects [0030]. Melief et al teach that the administration of CD40 binding molecules enhances the efficacy of anti-cancer vaccines comprising tumor specific peptides [0047]. Melief et al teach FGk45 as a CD40 activating antibody (line 5 of [0020]."

The Examiner admits that Melief et al do not teach the administration of a humanized S2C6 antibody for the treatment of cancer. In the previous Office Action dated June 4, 2003, the Examiner admitted that Melief et al did not teach the administration of a chimeric S2C6 antibody.

> The Examiner *alleges* that de Boer teaches:
>
> "that anti-CD40 antibodies known in the art [prior to the disclosure of de Boer] have a stimulatory effect on human B cells (column 2, lines 45-46 and 62-64). de Boer teaches that the prior art anti-CD40 antibodies mimic the effect of T-helper

> cells and thus can replace the T cell helper signal (column 2, lines 51-59). de Boer teaches 'new' antibodies such as 5D12, 3C6, and 3A8 which differ from the prior art anti-CD40 antibodies in that the new antibodies inhibit the B-cell stimulatory response (column 2, lines 62-67). de Boer teaches S2C6 as an "old" antibody (in contrast to the "new" antibodies) which stimulates B-cell proliferation (column 17, lines 57-62, and the description for Figures 5 and 6). de Boer teaches that the "new" antibodies can inhibit stimulatory signals elicited by the "triggering" of CD40 with another antibody (column 18, lines 36-40). One of skill in the art would reasonably conclude that the "old" S2C6 antibody "triggers" CD40. de Boer teaches that the administration of humanized versions of the "new" antibodies would be efficacious in the treatment of antibody-mediated autoimmune diseases (column 3, lines 52-65 and column 4, lines 14-19)."

The Examiner admits that S2C6 and the antibodies disclosed by de Boer are different in structure and function (page 8 of the Office Action, lines 12-14).

A. No Motivation to Combine References

Applicants submit that the subject matter of these claims is not obvious over this combination of references because the Examiner has provided no motivation for making this combination, as required by MPEP 2142-2144. These sections of the MPEP specifically establish the requirement that there must be a suggestion or motivation to modify the cited references to support a rejection for obviousness. As stated in the MPEP:

> "[o]bviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art." (MPEP 2143.01, quoting from In re Fine, 837 F.2d 1071, 5 U.S.P.Q. 2d 1596 (Fed. Cir. 1988).

Further, MPEP 2143.01 citing In re Mills, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990 :

"[t]he mere fact that references <u>can</u> be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." (emphasis in the original).

These MPEP sections are in accord with numerous well-established precedents. *In re Geiger*, 815 F. 2d 686, 2 U.S. P. Q. 2d 1271 (Fed. Cir. 1987); *N.V. Akzo v. E.I. du Pont de Nemours*, 810 F.2d 1148, 1 U.S. P.Q. 2d 1704 (Fed. Cir 1987); *In re Farrell*,

853 F.2d 894, 7 U.S.P.Q. 2d 1673 (Fed. Cir. 1988). The Examiner is using impermissible hindsight and is making a piecemeal rejection. The Examiner is using no less than 10 publications and/or patents in the Office Action to attempt to render obvious the claims. The Applicants respectfully assert that the Examiner cannot, with the present application and claims as a guide, piece together a variety of publications which by themselves or in combination have no motivation to combine, to render the present claims obvious. It is wrong to use the claims under consideration as a guide through the maze of publications and patents, combining the right publications and patents in the right way so as to achieve the result of the claims in the current application. *Orthopedic Equipment Co. v. United States, 702 F.2d 1005, 217 U.S.P.Q. 193 (Fed.Cir. 1983).*

B. Improper to Combine References Which Teach Away from the Claims; de Boer does not satisfy the deficiencies of Melief and the combination of Melief and de Boer cannot render the claims 26, 27, 33, 41, 42, 44-48, 50, 52-55, 59-65, 68, 75-77 and 83-93 obvious under 35 U.S.C. 103(a).

It is improper with an obviousness rejection to combine two references if one of the references teaches away from the claimed invention. Where a reference warns against rather than teaches the invention, one cannot be expected to combine it with another teaching. (In re Fine, 837 F.2d 1071, 5 USPQ 1596 (Fed. Cir. 1988). As stated in paragraph 2141.02 of the MPEP, "a prior art reference must be considered in its entirety, i.e., as a whole, including portions which would lead away from the claimed invention." MPEP paragraph 2141.02 provides the following example of a teaching away:

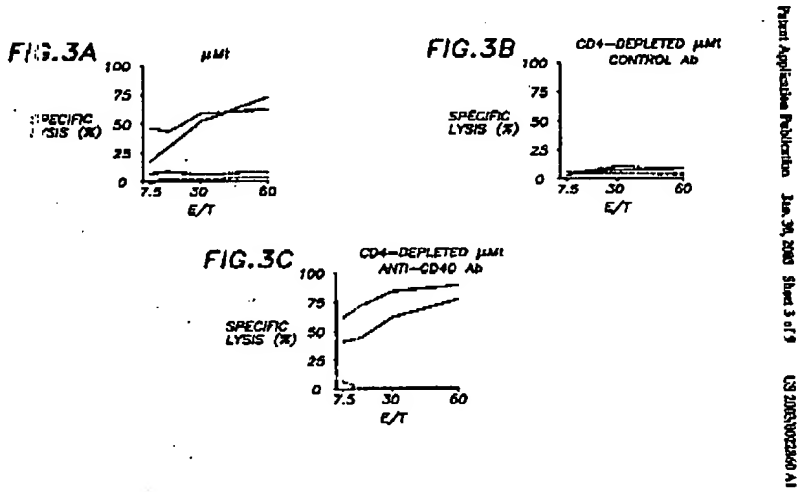
> Claims were directed to a process of producing a porous article by expanding shaped, unsintered, highly crystalline poly(tetrafluoroethylene) (PTFE) by stretching said PTFE at a 10% per second rate to more than five times the original length. The prior art teachings with regard to unsintered PTFE indicated the material does not respond to conventional plastics processing, and the material should be stretched slowly. A reference teaching rapid stretching of conventional plastic polypropylene with reduced crystallinity combined with a reference teaching stretching unsintered PTFE would not suggest rapid stretching of highly crystalline PTFE, in light of the disclosures in the art that teach away from the invention, i.e., that the conventional polypropylene should have reduced crystallinity before stretching, and that PTFE should be stretched slowly.

A reference may be said to teach away when a person of ordinary skill, upon reading it, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path taken by the inventor (Monarch Knitting Mach. Corp. v. Sulzer Morat Gmbh, 139 F.3d 877, 45 USPQ 1977 (Fed. Cir. 1998); Para-Ordnance Mfg. v. SGS Importers Int'l, Inc., 73 F.3d 1085, 37 USPQ 1237 (Fed. Cir. 1995); In re Gurley, 27 F.3d 551, 31 USPQ 1130 (Fed. Cir. 1994).) Melief et al teach away from the claimed invention because Melief et al *specifically and particularly teach away from* a *CD40 on B-cells* (see paragraph [0040] of Melief).

Melief et al discusses the "licensing model" of CTL activation (*See* para. [0004], lines 1-11 of Melief et al.). Briefly, in the licensing model, T-helper cells recognize a specific antigen on professional antigen-presenting cells (APCs), and deliver a signal that activates, or 'licenses', the APC (*See* para. [0004], lines 5-11 of Melief et al). This activated APC can then stimulate T-killer cells to mount a response against that antigen. More particularly, Cytotoxic T lymphocytes (CTLs) which carry the CD8 antigen recognize antigens that are presented on target cells by the class I major histocompatibility complex. CTLs are responsible for the killing of antigen-bearing target cells, such as virus-infected cells or cancer cells (see para. [0003], lines 1-3 of Melief et al.). Although CTL effectors can act alone when killing target cells, their differentiation from naive CD8-positive T cells is often dependent on 'help' from CD4-positive helper T (T_H) cells. Melief et al describe that "... the T-helper cell is not providing helper signals directly to the CTL...but rather, the T-helper cell is providing a signal to the DC that induces yet uncharacterized cell surface and/or soluble molecules that can activate CTL in the absence of T-helper cells." (see para. [0002], lines 9-14). To generate an immune response, antigen-specific T-helper and T-killer cells must find each other. They are brought together by an antigen-loaded cell, such as a dendritic cell (see para [0002] lines 14-16 and para. [0007], lines 6-8 of Melief et), that displays antigens to both. As stated in Melief "[t]he signal provided by the T-helper cell to the DC is mediated by CD40-CD40L." Para. [0002], lines 15-17. In the licensing model, the T helper cell can first engage and 'condition' the dendritic cell which then becomes empowered to stimulate a killer cell. As stated in Melief et al "interaction between T-helper cell and DC through the CD40-CD40L binding results in activation of the DC, thereby enabling the DC to

efficiently prime naïve CTL" (para. [0004], lines 15-18 of Melief et al.) wherein the T-helper cells express CD40L (see para. [0010, lines 7-9 of Melief et al) and the DC cells express CD40 (see para. [0007], lines 6-8 of Melief et al). Melief et all discusses "*...the CD40 pathway on DC is responsible for the induction of anti-tumor CTL responses.*" (see para. [0007, lines 6-8 of Melief et al.) (emphasis added).

This "licensing model" is further elucidated in Figures 3a, 3b, and 3c. Paragraph [0017] of Melief et al. The legend for Figure 3 is "*B cells are not essential* as cross-priming APCs or for anti-CD40 mediated restoration of cross-priming." (emphasis added). Figures 3a, 3b, and 3c are reproduced below:



The experiment represented in Figures 3a, 3b, 3c was conducted to investigate whether B cells had a role in the restoration of CTL priming by treatment with CD40 activating antibodies. As one can see in Figure 3c, which depicits cell lysis approaching about 75% to 90% in CD4 depleted/B cell deficient/treated with the CD-40 activating antibody FGK45 mice, shows that *B cells are not necessary* in the restoration of CTL priming by treatment with CD40 activating antibodies.

Figure 3a shows specific percent lysis *versus* effector/target ratio from a study of spenocytes taken from untreated B6 MT mice, *lacking mature B cells*, which were immunized with the activating peptide Ad5EI-BALB/c MECs (mouse embryo cells expressing the human adenovirus type 5 early region 1). The spenocytes were tested for

E1B-specific CTL (cytotoxic T lymphocytes) activity on synergestic MEC target cells loaded with either the $E1B_{192-200}$ peptide (solid lines) or the HPV $E7_{49-57}$ control peptide (dashed lines). Figure 3a shows that cross-priming of E1B-specific CTLs did not require mature B cells. (para. [0040], lines 6-7).

Figure 3b shows specific percent lysis *versus* effector/target ratio from a study of spenocytes taken from CD4-depleted *B-cell-deficient* B6 MT mice, lacking mature B cells, which were immunized with the activating peptide Ad5EI-BALB/c MECs. The mice received an isotype control antibody. The spenocytes were tested for E1B-specific CTL activity on synergestic MEC target cells loaded with either the $E1B_{192-200}$ peptide (solid lines) or the HPV $E7_{49-57}$ control peptide (dashed lines). Figure 3b shows that the B cell deficient mice, when depleted of CD4+ cells, did not generate E1B-specific CTL response. This is unlike the mice in Figure 3a, which had CD4+ cells, and no mature B cells, but which still showed cross-priming.

Figure 3c shows specific percent lysis *versus* effector/target ratio from a study of spenocytes taken from CD4-depleted *B-cell-deficient* B6 MT mice, lacking mature B cells, which were immunized with the activating peptide Ad5EI-BALB/c MECs. The mice received the CD-40 activating antibody FGK45. The spenocytes were tested for E1B-specific CTL activity on synergestic MEC target cells loaded with either the $E1B_{192-200}$ peptide (solid lines) or the HPV $E7_{49-57}$ control peptide (dashed lines). Activation through CD40 with the FGK45 monoclonal antibody completely restored the capacity of CD4-depelted B6 MT mice to prime E1B-specific CTLs.

Therefore, Melief et al does not teach CD40 being found on B cells. Rather, in this licensing model, CD40 is found on dendritic cells.

Figures 3a, 3b, and 3c are further described in Melief et al in Example 1 "Signaling through CD40 can replace $CD4^+$ helper T cells in CTL, priming." (see para. [0037]-[0040] of Melief et al.) Melief et al actually *teach away from* a molecule as claimed which "increases the binding of CD40 ligand to cell surface CD40 *on B cells*." Melief et al, in paragraph [0040] state as follows "...B cells *are not required* as APC or accessory cells for cross-priming in this model system, *nor are they required* for CD40-mediated restoration of cross priming of CTLs in the absence of CD4+ helper T cells." (emphasis added). To address the suggestion that B cells have a role in the restoration of

CTL priming by treatment with CD40 activating antibodies (the only example in Melief et al of an activating antibody being FGK45 monoclonal antibody), B6 MT mice (mice which lack mature B cells) were immunized with allogeneic Ad5EI-BALB/ MECs. Melief et al allege that mature B cells were not needed for cross priming of EIB-specific CTLs. Even in the absence of CD4+ cells in mice with depleted B cells, B cells were not needed for the priming of EIB-specific CTLs in the presence of FGK45 monoclonal antibody. Thus, Melief et al teach away from a molecule which increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45 % since B cells are not needed in Melief's model system.

This is directly opposite of what is taught in de Boer, i.e. that CD40 is found on B-cells. Since the Melief et al and de Boer teach opposite things, the two references cannot be properly combined. de Boer does not satisfy the deficiencies of Melief et al and one would not look to the disclosure of de Boer to satisfy the deficiencies of Melief et al. First, Melief et al teach away from CD40 being found on the surface of B-cells. In direct opposition, de Boer teaches that CD40 is found on the surface of B-cells. Second, de Boer places S2C6 in the group of antibodies which stimulates human B-cells. However, Melief does not even disclose CD40 on B-cells, let alone the stimulation of B-cells. The functions of the antibodies of de Boer compared to the function of the "old" antibodies, as admitted by the Examiner on page 8 of the current Office Action, are in opposition. The de Boer antibodies inhibit stimulation of B-cells whereas the "old" antibodies, into which the Examiner groups S2C6, stimulate B cells. However, B-cells are not even required in the process of antigen presentation as described in Melief et al. One who is seeking to increase the proliferation of B-cells, as antibody S2C6 does, would not look to two disclosures which disclose (a) no need for B-cells (Melief et al) and (b) the inhibition of the proliferation of B-cells (de Boer). Third, de Boer teaches that the antibodies of his invention **block** CD40L/CD40 interaction (col. 12, lines 66-67 through col. 13, lines 1-2 of de Boer) rather than "increases the binding of CD40 ligand to cell surface CD40 *on B cells*" as claimed. Therefore, Applicants respectfully assert that claims 26, 27, 33, 41, 42, 44-48, 50, 52-55, 59-65, 68, 75-77 and 83-93 are unobvious under 35 U.S.C. 103(a) over Melief et al in view of de Boer. Applicants respectfully request withdraw of the rejection.

Claim 26

The Examiner alleges that Melief et al in view of de Boer render claim 26 obvious. Claim 26 recites a molecule "...which molecule...increases the binding of CD40 ligand to cell surface CD40 on B cells...". In Example 1 of Melief et al, relied on by the Examiner, Meliefet al teach away from CD40 on B cells (see paragraph [0040] lines 12-16). This is contrary to what is recited in claim 26.

Further, claim 26 recites "...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...". Melief et al, alone or in combination, do not teach or suggest a molecule which increases the binding of CD40 ligand to cell surface CD40 on B cells *by at least 45%*. In stark contrast, Melief et al actually *teach away from* a molecule which "increases the binding of CD40 ligand to cell surface CD40 *on B cells*." Melief et al, in paragraph [0040] state as follows "...B cells *are not required* as APC or accessory cells for cross-priming in this model system, *nor are they required* for CD40-mediated restoration of cross priming of CTLs in the absence of CD4+ helper T cells." (emphasis added). Melief et al teach away from a molecule which increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45 % since B cells are not needed in Melief's model system. As discussed above, de Boer cannot satisfy the deficiencies of Melief et al. Applicants respectfully assert that claim 26 is unobvious under 35 U.S.C. 103(a) over Melief et al in view of de Boer.

Claim 27

The Examiner alleges that Melief in view of de Boer renders claim 27 obvious. Claim 27 recites "...administering to the subject ...a purified protein which...increases the binding of CD40 ligand to cell surface CD40 on B cells...". In Example 1 of Melief, on which the Examiner relies, Melief teaches away from CD40 on B cells (see paragraph [0040] lines 12-16) which is contrary to what is recited in claim 27.

Claim 27 recites "...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...". Melief et al, alone or in combination, do not teach or suggest a molecule which increases the binding of CD40 ligand to cell surface CD40 on B cells *by at least 45%*. In stark contrast, Melief et al actually *teach away from* a molecule which "increases the binding of CD40 ligand to cell surface CD40 *on B cells*." Melief et

al, in paragraph [0040] states as follows "...B cells *are not required* as APC or accessory cells for cross-priming in this model system, *nor are they required* for CD40-mediated restoration of cross priming of CTLs in the absence of CD4+ helper T cells." (emphasis added). Melief et al teach away from a molecule which increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45 % since B cells are not needed in Melief's model system. As discussed above, de Boer cannot satisfy the deficiencies of Melief et al. Applicants respectfully assert that claim 26 is unobvious under 35 U.S.C. 103(a) over Melief et al in view of de Boer.

Claims 33, 41, 42, 44-48, 50, and 52-55

The Examiner alleges that Melief et al in view of de Boer render claim 33, 41, 42, 44-48, 50, and 52-55 obvious. As claims 33, 41, 42, 44-48, 50, and 52-55 are dependant claim from claims 26 or 27, and independent claims 26 and 27 as discussed above are non-obvious over Melief et al in view of de Boer, any dependant claims are also non-obvious and allowable.

Claim 59

Claim 59 recites "... increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45...". As discussed above, Melief et al, neither alone nor in combination, teach or suggest a molecule which "increases the binding of CD40 ligand to cell surface CD40 *on B cells by at least 45%*." Further, Melief actually *teaches away from* a molecule which "increases the binding of CD40 ligand to cell surface CD40 *on B cells*."

Claim 60

Claim 60 recites "...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45...". As discussed above, Melief et al, neither alone nor in combination, teach or suggest a molecule which "increases the binding of CD40 ligand to cell surface CD40 *on B cells by at least 45%*." Further, Melief et al actually *teach away from* a molecule which "increases the binding of CD40 ligand to cell surface CD40 *on B cells*."

Claim 61

Claim 61 recites "...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45...." As discussed above, Melief et al, neither alone nor in combination, teach or suggest a molecule which "increases the binding of CD40 ligand to cell surface CD40 *on B cells by at least 45%*". Further, Melief et al actually *teach away from* a molecule which "increases the binding of CD40 ligand to cell surface CD40 *on B cells*."

Claim 62

Claim 62 is dependant from independent claim 61. As claim 62 is a dependant claim from an allowable independent claim 61, claim 62 is therefore also allowable.

Claim 63

Claim 63 recites "... a molecule that... increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45...." As discussed above, Melief et al, neither alone nor in combination, teach or suggest a molecule which "increases the binding of CD40 ligand to cell surface CD40 *on B cells by at least 45%.*" Further, Melief et al actually *teach away from* a molecule which "increases the binding of CD40 ligand to cell surface CD40 *on B cells*."

Claim 64

Claim 64 recites "...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45...." As discussed above, Melief et al, neither alone nor in combination, teach or suggest a molecule which "increases the binding of CD40 ligand to cell surface CD40 *on B cells by at least 45%*. Further, Melief et al actually *teach away from* a molecule which "increases the binding of CD40 ligand to cell surface CD40 *on B cells*."

Claims 65, 68, 75, 76, 77, 82-114

Claims 65, 68, 75, 76, 77, 82-114 all depend from non-obvious independent claims 26, 27, 37. Claims 65, 68, 75, 76, 77, 82-114 are dependent claims and

distinguish for at least the same reasons as their independent base claims and are therefore also allowable.

9. **Paragraph 14 of the Office Action – Rejection of Claims 26, 27, 33,41, 42, 44--50, 52-56, 57, 59-65, 68, and 75-78 under 35 U.S.C. Section 103(a) as being unpatenable over Melief (U.S. application No. 2003/0022860) and de Boer (U.S. 5,874,082) in view of Clark (Protein Engineering of Antibody Molecules for Prophylactic and Therapeutic Applications in Man).**

The Examiner rejected claims 26, 27, 33,41, 42, 44--50, 52-56, 57, 59-65, 68, and 75-78 under 35 U.S.C. Section 103(a) as being unpatenable over Melief et al (U.S. application No. 2003/0022860) and de Boer (U.S. 5,874,082) in view of Clark. The Examiner recites that claims 49, 56, and 78 specify that the antibodies which bind to CD40 are human antibodies. The Examiner alleges that Clark teaches "the generation of human antibodies from combinatorial libraries of human immunoglobulin repertories." The Examiner alleges that based on the teaching of Clark it would have been obvious to screen a combinatorial library of human immunoglobulin genes to identify a human antibody which binds to the S2C6 epitope of CD40. The Applicants respectfully traverse this rejection.

Claim 49

The Examiner rejected claims 26, 27, 33,41, 42, 44--50, 52-56, 57, 59-65, 68, and 75-78 under 35 U.S.C. Section 103(a) as being unpatenable over Melief et al (U.S. application No. 2003/0022860) and de Boer (U.S. 5,874,082) in view of Clark. Clark merely suggests IgG isotypes without any suggestion of molecules comprising the sequences of S2C6 heavy chain CDRs or variable region (or closely related sequences) fused to a heterlogous molecule. As claim 49 is a dependant claim of claim 26 or 27, and independent claims 26 and 27 as discussed above are non-obvious over Melief et al in view of de Boer, and Clark does not satisfy any deficiencies of Melief et al and de Boer, any dependant claims are also non-obvious and allowable.

Claim 56

The Examiner rejected claims 26, 27, 33,41, 42, 44--50, 52-56, 57, 59-65, 68, and 75-78 under 35 U.S.C. Section 103(a) as being unpatenable over Melief et al (U.S. application No. 2003/0022860) and de Boer (U.S. 5,874,082) in view of Clark. As claim 56 is a dependant claim of claim 27, and independent claim 27 as discussed above is non-obvious over Melief et al in view of de Boer, and Clark does not satisfy any deficiencies of Melief et al and de Boer, any dependant claims are also non-obvious and allowable.

Claim 78

The Examiner rejected claims 26, 27, 33,41, 42, 44--50, 52-56, 57, 59-65, 68, and 75-78 under 35 U.S.C. Section 103(a) as being unpatenable over Melief et al (U.S. application No. 2003/0022860) and de Boer (U.S. 5,874,082) in view of Clark. As claim 78 is a dependant claim of claim 61, and independent claim 61 as discussed above is non-obvious over Melief et al in view of de Boer, and Clark does not satisfy any deficiencies of Melief et al and de Boer, any dependant claims are also non-obvious and allowable.

10. **Paragraph 15 of the Office Action – Rejection of Claims 26, 27, 33, 41, 42, 44-48, 50, 52-55, 59-65, 68, 75-77, 83-96, and 100-108 under 35 U.S.C. 103(a) over Funakoshi et al in view of Bjorck et al and de Boer (US Patent No. 5,874,082) as evidenced by Uckun et al.**

The Examiner rejected claims 26, 27, 33, 41, 42, 44-48, 50, 52-55, 59-65, 68, 75-77, 83-96, and 100-108 under 35 U.S.C. 103(a) over Funakoshi et al in view of Bjorck et al and de Boer (US Patent No. 5,874,082) as evidenced by Uckun et al. Applicants respectfully traverse this rejection.

Neither Funakoshi (see pg 2793 of Funakoshi, submitted in the IDS dated Nov. 28, 2000 as document AZ, title of Reference No. 11, which discloses that "CD40 MABS M2 and M3 *inhibit* CD40L binding and function") nor Uckun (which discloses CD40 antibody G28-5, page 2450, col 1, line 27; see also pg 3, lines 34-36 and page 54, lines 24-29 of the present application where it is disclosed that G28-5 *does not potentiate* CD40/CD40L interaction) nor Bjorck (see page 434, right hand column and Table 4) teach increased binding of CD40 to CD40L as claimed. Actually, all three teach away

from antibodies which increase the binding of CD40L to CD40 as claimed in independent claims 26, 27, 59, 60, 61, 63 and 64.

The Examiner states that the Applicants have addressed Bjorck before in this application. However, Bjorck has not previously been applied in this application and the Applicants have not addressed it previously in this application. The Examiner has perhaps confused this divisional application with its parent application, 09/328,296.

Bjorck specifically discloses *the inhibition of binding* of CD40 to CD40 ligand on page 434, second column, lines 14-19 as follows "[w]hen investigating the ability of the antibodies to interfere with binding of CD40-ligand all three mAb" (i.e. 17:40, mAb89, and S2C6) "*were to different extents able to do so*...." (emphasis added). Bjorck discloses that S2C6 blocked binding of CD40 to CD40L up to 60%.

de Boer does not satisfy the deficiencies of any of the three above references in failing to teach the increased binding of CD40 to CD40 ligand. de Boer does not teach or suggest an antibody which would increase the binding of CD40 to CD40 ligand. Therefore, this combination of references cannot render the claims 26, 27, 59, 60, 61, 63 and 64, nor any dependant claims therefrom, obvious. Applicants respectfully request withdraw of this rejection.

11. **Paragraph 16 of the Office Action - Rejection of Claims 26, 27, 33, 41, 42, 44-48, 50, 52-55, 58-66, 68, 75-77, 79, 80, and 83-111 under 35 U.S.C. 103(a) over Francisco et al (The Journal of Biological Chemistry, 1997, Vol. 272, pp. 24165-24169) in view of Paulie et al (Cancer Immunology, Immunotherapy, 1985, Vol. 20, pp. 23-28) and de Boer (US Patent No. 5,874,082) and Schlom (Molecular Foundations of Oncology, S. Broader, Ed. 1991, pp. 95-145).**

The Examiner rejected claims 26, 27, 33, 41, 42, 44-48, 50, 52-55, 58-66, 68, 75-77, 79, 80, and 83-111 under 35 U.S.C. 103(a) over Francisco et al in view of Paulie et al and de Boer (US Patent No. 5,874,082) and Schlom. The Applicants respectfully traverse this rejection.

The Examiner alleges that Francisco teaches "bryodin fused to the sFv fragment of the G28.5 antibody which binds CD40 is cytotoxic to a non-Hodgkin's lymphoma cell line, a multiple myeloma cell line, a B-cell leukemia and a Hodgkin's disease cell line. Francisco et al teaches that all these cell lines express CD40." Further, the Examiner alleges that Francisco et al teaches that "because bryodin kills cancer cells, it is concluded that bryodin is a chemotherapeutic agent. Francisco et al also teach that G28.5 fused to Pseudemonas exotoxin was toxic to lung, breast, colon and ovarian carcinoma cell in vitro."

The Examiner alleges that Paulie et al teach that "S2C6 antigen is found on bladder cancer cells and on B lymphocytes." The Examiner further alleges that Paulie teaches that "the S2C6 epitope is part of the CD40 receptor (abstract, lines 1-3)." The Applicants respectfully assert that the abstract of Paulie does not teach that "the S2C6 epitope is part of the CD40 receptor" as suggested by the Examiner.

The Examiner alleges that de Boer teaches "how to make humanized anti-CD40 antibodies." The Examiner admits that de Boer does not teach how to make a humanized anti-CD40 S2C6 antibody.

The Examiner alleges that Schlom teaches the answer to the HAMA response is "humanization of murine antibodies." The Examiner further alleges that Schlom teaches that "single chained antibodies and Fab antibody fragments have increased ability to penetrate through tumor masses in contrast to whole antibodies."

The Examiner has not shown where, either alone nor in combination, Francisco et al, Paulie et al, de Boer and Schlom et al teach or suggest "increases the binging of CD40 ligand to cell surface CD40 on B cells by at least 45%" as claimed in independent claims 26, 27, 58-61, 63 and 64. Accordingly, the present claims would not be rendered obvious by the cited articles. Claims 33, 41, 42, 44-48, 50, 52-55, 62, 65, 66, 68, 75-77, 79, 80 and 83-111 are dependent claims and distinguish for at least the same reasons as their independent base claims. Therefore, the Applicants respectfully requests that the instant obviousness rejection be withdrawn.

Claim 26

Claim 26 recites "administering to a subject an amount of a molecule ...which...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...". As discussed above, Francisco et al in view of Paulie et al, de Boer, and Schlom, neither alone nor in combination, teach or suggest "...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...".

Claim 27

Claim 27 recites "...a purified protein, which protein...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...". As discussed above, Francisco et al in view of Paulie et al, de Boer, and Schlom, neither alone nor in combination, teach or suggest "...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...". Francisco et al in view of Paulie et al, de Boer, and Schlom cannot satisfy the deficiencies discussed above with regards to the rejections over Melief et al alone or in combination with various patents and articles cited by the Examiner.

Claims 33, 41, 42, 44-48, 50, and 52-55

Claim 33 is dependant from allowable independent claims 26 or 27 and therefore is also allowable. Claim 41 is dependant from allowable independent claim 26 and is therefore also allowable. Claim 42 is dependant from claim 38 which is dependant from allowable independent claim 26, claim 39 which is dependant from allowable independent claim 27, and claim 40 which is dependant from allowable independent claim 37 which, as discussed above, recites "...which protein increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...", and therefore is also allowable. Claim 44 is dependant from allowable independent claim 25 and therefore is also allowable. Claims 45-48, and 50, depend, directly or indirectly, from claim 44 which is dependant on allowable independent claim 26, and therefore claims 45-48, and 50 are also allowable. Claim 52 is dependant from allowable independent claim 27 and therefore is also allowable. Claims 53-55 depend, directly or indirectly, from claim 52 which is dependant on allowable independent claim 27, and is therefore also allowable.

Claim 58

Claim 58 recites "...a molecule...which...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...". As discussed above, Francisco et al in view of Paulie et al, de Boer, and Schlom, neither alone nor in combination, teach or suggest "...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...". Francisco et al in view of Paulie et al, de Boer, and Schlom cannot satisfy the deficiencies discussed above with regards to the rejections over Melief et al alone or in combination with various patents and articles cited by the Examiner.

Claim 59

Claim 59 recites "...a molecule...which...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...". As discussed above, Francisco et al in view of Paulie et al, de Boer, and Schlom, neither alone nor in combination, teach or suggest "...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...". Francisco et al in view of Paulie et al, de Boer, and Schlom cannot satisfy the deficiencies discussed above with regards to the rejections over Melief alone or in combination with various patents and articles cited by the Examiner.

Claim 60

Claim 60 recites "a protein... which...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...". As discussed above, Francisco et al in view of Paulie et al, de Boer, and Schlom, neither alone nor in combination, teach or suggest "...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...". Francisco et al in view of Paulie et al, de Boer, and Schlom cannot satisfy the deficiencies discussed above with regards to the rejections over Melief et al alone or in combination with various patents and articles cited by the Examiner.

Claim 61

Claim 61 recites "a protein... which...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...". As discussed above, Francisco et al in view of Paulie et al, de Boer, and Schlom, neither alone nor in combination, teach or

suggest "...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...". Francisco et al in view of Paulie et al, de Boer, and Schlom cannot satisfy the deficiencies discussed above with regards to the rejections over Melief et al alone or in combination with various patents and articles cited by the Examiner.

Claim 62

Claim 62 is dependant from allowable independent claim 61 and is therefore also allowable.

Claim 63

Claim 63 recites "a molecule... which...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...". As discussed above, Francisco et al in view of Paulie et al, de Boer, and Schlom, neither alone nor in combination, teach or suggest "...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...". Francisco et al in view of Paulie et al, de Boer, and Schlom cannot satisfy the deficiencies discussed above with regards to the rejections over Melief et al alone or in combination with various patents and articles cited by the Examiner.

Claim 64

Claim 64 recites "a molecule... which...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...". As discussed above, Francisco et al in view of Paulie et al, de Boer, and Schlom, neither alone nor in combination, teach or suggest "...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...". Francisco et al in view of Paulie et al, de Boer, and Schlom cannot satisfy the deficiencies discussed above with regards to the rejections over Melief et al alone or in combination with various patents and articles cited by the Examiner.

Claims 65 and 66

Claim 65 is dependant from allowable independent claim 64 and is therefore also allowable. Claim 66 is dependant from allowable independent claims 58 and 59 and is therefore also allowable.

Claim 68

Claim 68 is dependant from allowable independent claim 61 and is therefore also allowable.

Claims 75-77

Claim 75 is dependant from allowable independent claim 61 and is therefore also allowable. Claims 76 and 77 depend, directly or indirectly, from claim 75 which is dependant on allowable independent claim 61, and are therefore also allowable.

Claim 79

Claim 79 is dependant from allowable independent claim 61 and is therefore also allowable.

Claim 80

Claim 80 is dependant from dependant claim 75. Claim 75 is dependant from allowable independent claim 61. As claim 80 is indirectly dependant from allowable independent claim 61, it is also allowable.

Claims 83-111

Claims 83-111 are dependant from, indirectly or directly, allowable independent claims 26, 27, 37, 58, 59, 60, 61, 63, and 64, and are therefore also allowable.

12. **Paragraph 17 of the Office Action - Rejection of Claims 26, 27, 33, 41, 42, 44-48, 50, 52-55, 59-65, 68, 75-77, 83-93, 97-99 and 109-144 under 35 U.S.C. 103(a) as being unpatentable over Melief et al and de Boer as applied to claims 26, 27, 33, 41, 42, 44-48, 50, 52-55, 59-65, 68, 75-77 and 83-93 above, and further in view of Slingluff et al (WO 98/33810).**

The Examiner rejected claims 26, 27, 33, 41, 42, 44-48, 50, 52-55, 59-65, 68, 75-77, 83-93, 97-99 and 109-144 under 35 U.S.C. 103(a) as being unpatentable over Melief et al and de Boer as applied to claims 26, 27, 33, 41, 42, 44-48, 50, 52-55, 59-65, 68, 75-

77 and 83-93 above, and further in view of Slingluff et al (WO 98/33810). Applicants respectfully traverse this rejection.

The Examiner recites that "the combination of Melief et al and Bjorck et al" allegedly "render obvious a method of treating cancer comprising the administration of a humanized or chimeric S2C6 antibody in a vaccine comprising a CTL-activating tumor peptide...". Melief et al teach immune system upregulation whereas the antibody claimed in claim 26 is capable of action thru direct killing or killing thru natural killer cells. Melief et al teach away from this course of action. Melief et al recite "[i]t is preferable that the antibody be IgG4, IgG2, or other genetically mutated IgG or IgM which does not augment antibody dependant cellular cytotoxicity ... and complement mediated cytolysis." See Melief, para. [0030]. The Applicant is perplexed on where the Examiner believes the claims are directed to a vaccine or a vaccine comprising a CTL-activating tumor peptide. No mention of a vaccine or CTL-activating tumor peptide is made in the present claims. It appears that the Examiner merely found a document that mentioned bladder carcinoma and NCLSC and is attempting to apply the mere mention of these carnimomas to the claims.

Further, as discussed above, neither Melief et al alone nor in combination with de Boer or any of the other patents or articles cited by the Examiner teach or suggest "increases the binding of CD40 ligand to cell surface CD40 by at least 45%." Slingluff does not satisfy this deficiency. CD40 is not even mentioned in the application of Slingluff. Therefore, Applicants respectfully assert, in view of the comments above to the independent claims already addressing the combination of Melief et al and de Boer, the addition of Slingluff does not satisfy the deficiencies of these other patent or patent applications.

Applicants respectfully assert that Melief et al and de Boer as applied to claims 26, 27, 33, 41, 42, 44-48, 50, 52-55, 59-65, 68, 75-77 and 83-93 above, and further in view of Slingluff et al, either alone or in combination, do not render the present claims obvious. Therefore, the Applicants respectfully requests that the instant obviousness rejection be withdrawn.

13. **Paragraph 18 of the Office Action - Rejection of Claims 26, 27, 33, 41, 42, 44-48, 50, 52-55, 58-66, 68, 75-77, 79, 80, 83-114 are rejected under 35 U.S.C. 103(a) as being unpatentable over Francisco et al (The Journal of Biological Chemistry, 1997, Vol. 272, pp. 24165-24169) in view of Paulie et al (Cancer Immunology, Immunotherapy, 1985, Vol.20, pp. 23-28) and de Boer (U.S. Patent No. 5,874,082) and Schlom (Molecular Foundations of Oncology, S. Broader, Ed., 1991, pp. 95-134) as applied to claims 26, 27, 33, 41, 42, 44-48, 50, 52-55, 58-66, 68, 75-77, 79, 80, 83-96 and 100-108 above, and further in view of Kawaguchi et al (WO 98/33810).**

The Examiner rejected claims 26, 27, 33, 41, 42, 44-48, 50, 52-55, 58-66, 68, 75-77, 79, 80, 83-114 under 35 U.S.C. 103(a) as being unpatentable over Francisco et al in view of Paulie et al, de Boer and Schlom as applied to claims 26, 27, 33, 41, 42, 44-48, 50, 52-55, 58-66, 68, 75-77, 79, 80, 83-96 and 100-108 above, and further in view of Kawaguchi et al (WO 98/33810). The Applicant respectfully traverses this rejection.

The Examiner alleges that Kawaguchi et al teaches "that non-small cell lung cancers were found to express CD40 on the cell surface." As discussed above in section 10 of the present Amendment, the Examiner has not show where, either alone nor in combination, Francisco et al, Paulie et al, de Boer, and Schlom et al teach or suggest "increases the binding of CD40 ligand to cell surface CD40 *on B cells* by *at least 45%*" as claimed in independent claims 26, 27, 58-61, 63 and 64. Kawaguchi et al can not satisfy this deficiency. Kawaguchi et al fail to teach or suggest "CD40 on B cells" and "increases the binding of CD40 ligand to cell surface CD40... by at least 45%." Accordingly, the present claims would not be rendered obvious by the cited articles. Claims 33, 41, 42, 44-48, 50, 52-55, 62, 65, 66, 68, 75-77, 79, 80, 83-96 and 100-108 are dependent claims and distinguish for at least the same reasons as their independent base claims. Therefore, the Applicants respectfully requests that the instant obviousness rejection be withdrawn.

Claim 26

Claim 26 recites "administering to a subject an amount of a molecule ...which...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...". As discussed above, Francisco et al in view of Paulie et al, de Boer, and Schlom, and further in view of Kawaguchi et al, neither alone nor in combination, teach or suggest "...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...".

Claim 27

Claim 27 recites "...a purified protein, which protein...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...". As discussed above, Francisco et al in view of Paulie et al, de Boer, and Schlom, and further in view of Kawaguchi et al, neither alone nor in combination, teach or suggest "...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...".

Claims 33, 41, 42, 44-48, 50, and 52-55

Claim 33 is dependant from allowable independent claims 26 or 27 and therefore is also allowable Claim 41 is dependant from allowable independent claim 26 and is therefore also allowable. Claim 42 is dependant from claim 38 which is dependant from allowable independent claim 26, claim 39 which is dependant from allowable independent claim 27, and claim 40 which is dependant from allowable independent claim 37 which, as discussed above, recites "...which antibody increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...", and therefore is also allowable. Claim 44 is dependant from allowable independent claim 25 and therefore is also allowable. Claims 45-48, and 50, depend, directly or indirectly, from claim 44 which is dependant on allowable independent claim 26, and therefore claims 45-48, and 50 are also allowable. Claim 52 is dependant from allowable independent claim 27 and therefore is also allowable. Claims 53-55 depend, directly or indirectly, from claim 52 which is dependant on allowable independent claim 27, and is therefore also allowable.

Claim 58

Claim 58 recites "...a molecule...which...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...". As discussed above, Francisco et al in view of Paulie et al, de Boer, and Schlom, and further in view of Kawaguchi et al, neither alone nor in combination, teach or suggest "...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...".

Claim 59

Claim 59 recites "...a molecule...which...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...". As discussed above, Francisco et al in view of Paulie et al, de Boer, and Schlom, and further in view of Kawaguchi et al, neither alone nor in combination, teach or suggest "...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...".

Claim 60

Claim 60 recites "a protein... which...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...". As discussed above, Francisco et al in view of Paulie et al, de Boer, and Schlom, and further in view of Kawaguchi et al, neither alone nor in combination, teach or suggest "...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...".

Claim 61

Claim 61 recites "a protein... which...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...". As discussed above, Francisco et al in view of Paulie et al, de Boer, and Schlom, and further in view of Kawaguchi et al, neither alone nor in combination, teach or suggest "...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...".

Claim 62

Claim 62 is dependant from allowable independent claim 61 and is therefore also allowable.

Claim 63

Claim 63 recites "a molecule... which...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...". As discussed above, Francisco et al in view of Paulie et al, de Boer, and Schlom, and further in view of Kawaguchi et al, neither alone nor in combination, teach or suggest "...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...".

Claim 64

Claim 64 recites "a molecule... which...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...". As discussed above, Francisco et al in view of Paulie et al, de Boer, and Schlom, and further in view of Kawaguchi et al, neither alone nor in combination, teach or suggest "...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...".

Claims 65 and 66

Claim 65 is dependant from allowable independent claim 64 and is therefore also allowable. Claim 66 is dependant from allowable independent claims 58 and 59 and is therefore also allowable.

Claim 68

Claim 68 is dependant from allowable independent claim 61 and is therefore also allowable.

Claims 75-77

Claim 75 is dependant from allowable independent claim 61 and is therefore also allowable. Claims 76 and 77 depend, directly or indirectly, from claim 75 which is dependant on allowable independent claim 61, and are therefore also allowable.

Claim 79

Claim 79 is dependant from allowable independent claim 61 and is therefore also allowable.

Claim 80

Claim 80 is dependant from dependant claim 75. Claim 75 is dependant from allowable independent claim 61. As claim 80 is indirectly dependant from allowable independent claim 61, it is also allowable.

Claims 83-114

Claims 83-114 are dependant from, indirectly or directly, allowable independent claims 26, 27, 37, 58, 59, 60, 61, 63, and 64, and are therefore also allowable.

14. **Paragraph 19 of the Office Action - Rejection of Claims 26, 27, 33, 41, 42, 44-48, 50, 52-55, 59-65, 68, 75-77, 79, 80, 83-114 are rejected under 35 U.S.C. 103(a) as being unpatentable over Funakoshi et al (Blood, 1994, Vol. 83, pp. 2787-2794) and Bjorck et al (Immunology, 1994, Vol. 83, pp. 430-437) and de Boer (U.S. Patent No. 5,874,082) and by Uckun et al (Blood, 1990, Vol. 76, pp. 2449-2456) as applied to claims 26, 27, 33, 41, 42, 44-48, 50, 52-55, 59-65, 68, 75-77, 83-96 and 100-108 above, and further in view of the abstract of Kawaguchi et al (WO 98/33810).**

The Examiner rejected claims 26, 27, 33, 41, 42, 44-48, 50, 52-55, 59-65, 68, 75-77, 79, 80, 83-114 under 35 U.S.C. 103(a) as being unpatentable over Funakoshi et al, Bjorck et al, de Boer, and by Uckun et al as applied to claims 26, 27, 33, 41, 42, 44-48, 50, 52-55, 59-65, 68, 75-77, 83-96 and 100-108 above, and further in view of the abstract of Kawaguchi et al. Applicants respectfully traverse this rejection.

As discussed above in section 10 of this Amendment, neither Funakoshi et al, Uckun et al, or Bjorck et teach "increases the binding of CD40 ligand to cell surface CD40" as claimed. Actually, all three teach way from antibodies which increase the binding of CD40L to CD40 as claimed in independent claims 26, 27, 59, 60, 61, 63 and 64. Further, Bjorck et al disclose that S2C6 blocked binding of CD40 to CD40L up to

60%. de Boer does not teach or suggest an antibody which would increase the binding of CD40 to CD40 ligand. Therefore, this combination of references cannot render the claims 26, 27, 59, 60, 61, 63 and 64, nor any dependant claims therefrom, obvious. As discussed above in section 13 of this Amendment, Kawaguchi et al can not satisfy this deficiency. Kawaguchi et al fail to teach or suggest "CD40 on B cells" and "increases the binding of CD40 ligand to cell surface CD40... by at least 45%." Accordingly, the present claims would not be rendered obvious by the cited articles and patent. Claims 33, 41, 42, 44-48, 50, 52-55, 62, 65, 66, 68, 75-77, 79, 80, 83-96 and 100-108 are dependent claims and distinguish for at least the same reasons as their independent base claims. Therefore, the Applicants respectfully requests that the instant obviousness rejection be withdrawn.

Claim 26

Claim 26 recites "administering to a subject an amount of a molecule ...which...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...". As discussed above, Funakoshi et al, in view of Bjorck et al, de Boer, Uckun et al, and further in view of Kawaguchi, neither alone nor in combination, teach or suggest "...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...".

Claim 27

Claim 27 recites "...a purified protein, which protein...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...". As discussed above, Funakoshi et al, in view of Bjorck et al, de Boer, Uckun et al, and further in view of Kawaguchi, neither alone nor in combination, teach or suggest "...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...".

Claims 33, 41, 42, 44-48, 50, and 52-55

Claim 33 is dependant from allowable independent claims 26 or 27 and therefore is also allowable. Claim 41 is dependant from allowable independent claim 26 and is therefore also allowable. Claim 42 is dependant from claim 38 which is dependant from

allowable independent claim 26, claim 39 which is dependant from allowable independent claim 27, and claim 40 which is dependant from allowable independent claim 37 which, as discussed above, recites "...which antibody increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...", and therefore is also allowable. Claim 44 is dependant from allowable independent claim 25 and therefore is also allowable. Claims 45-48, and 50, depend, directly or indirectly, from claim 44 which is dependant on allowable independent claim 26, and therefore claims 45-48, and 50 are also allowable. Claim 52 is dependant from allowable independent claim 27 and therefore is also allowable. Claims 53-55 depend, directly or indirectly, from claim 52 which is dependant on allowable independent claim 27, and is therefore also allowable.

Claim 59

Claim 59 recites "...a molecule...which...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...". As discussed above, Funakoshi et al, in view of Bjorck et al, de Boer, Uckun et al, and further in view of Kawaguchi, neither alone nor in combination, teach or suggest "...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...".

Claim 60

Claim 60 recites "a protein... which...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...". As discussed above, Funakoshi et al, in view of Bjorck et al, de Boer, Uckun et al, and further in view of Kawaguchi, neither alone nor in combination, teach or suggest "...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...".

Claim 61

Claim 61 recites "a protein... which...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...". As discussed above, Funakoshi et al, in view of Bjorck et al, de Boer, Uckun et al, and further in view of Kawaguchi, neither alone nor in combination, teach or suggest "...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...".

Claim 62

Claim 62 is dependant from allowable independent claim 61 and is therefore also allowable.

Claim 63

Claim 63 recites "a molecule... which...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...". As discussed above, Funakoshi et al, in view of Bjorck et al, de Boer, Uckun et al, and further in view of Kawaguchi, neither alone nor in combination, teach or suggest "...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...".

Claim 64

Claim 64 recites "a molecule... which...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...". As discussed above, Funakoshi et al, in view of Bjorck et al, de Boer, Uckun et al, and further in view of Kawaguchi, neither alone nor in combination, teach or suggest "...increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45%...".

Claim 65

Claim 65 is dependant from allowable independent claim 64 and is therefore also allowable.

Claim 68

Claim 68 is dependant from allowable independent claim 61 and is therefore also allowable.

Claims 75-77

Claim 75 is dependant from allowable independent claim 61 and is therefore also allowable. Claims 76 and 77 depend, directly or indirectly, from claim 75 which is dependant on allowable independent claim 61, and are therefore also allowable.

Claims 83-114

Claims 83-114 are dependant from, indirectly or directly, allowable independent claims 26, 27, 37, 58, 59, 60, 61, 63, and 64, and are therefore also allowable.

Conclusion

Applicants assert that in view of the above amendments and remarks, the Examiner's rejections have been successfully overcome and the application is in condition for allowance. Applicants respectfully request further action commensurate therewith.

Respectfully submitted,

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